Disturbances in the Renal Regulation of Fluid and Electrolyte Balance in Acute Infectious Diseases

By

M. GALAMBOS and T. VITTAY

László Hospital (Director, Dr. J. ROMÁN), Budapest

(Received August 29, 1961)

There are numerous observations to indicate that disturbances of renal compensatory function occur not only in the so-called organic renal diseases, but also in the widest variety of acute infections, nervous and metabolic disorders. Recent investigations have emphasized the significance of tubular function, in the first place. It has been shown that the fine regulatory activity of the kidney is based chiefly on tubular function, and that an impairment of this may give rise to various pathologic conditions and the disturbance of normal balance.

In a study of the role of the kidney in the development of the metabolic disorders accompanying acute infections, little help can be expected from the usual tests of renal function. The clearance methods require ample diuresis; in conditions associated with oliguria they supply limited information. Besides, one is reluctant to administer clearance substances in severe conditions, especially in infants and children. It is often difficult to collect urine from a child quantitatively, and this may account for the considerable divergence of the results for the child and the adult.

In the knowledge of the above difficulties the efforts to obtain information as to the regulatory and compensatory activity of the kidney from a detailed analysis of the urine merit attention [22, 24, 25, 41]. Although this procedure does not solve all the afore-mentioned problems, it does supply information concerning the most fundamental renal activities, notably concentration, acidification, ammonia formation, base conservation, etc.

In our investigations we have always laid emphasis upon the parallel examination of urine and serum by means of the ionograms, this being the only way to gain insight not only into the activities, but also into the tasks of the kidney.

In the present paper we shall report on five different cases treated at our Department, in order to present illustrative examples of the single types of impaired function, with special attention to the disorder of tubular activity We shall analyse one case each of diffuse glomerulonephritis, acute dehydration, hypernatraemic encephalitis, hypernatraemic shock, and one of acute tubular necrosis.

The evidence to be presented has been based on detailed serial tests in every case.

Methods

Blood and urine were tested in every case. In most cases the urine obtained through an indwelling catheter was collected under neutralized toluol quantitatively for several, if possible for 24, hours.

The blood samples were tested for standard bicarbonate, sodium, potassium, chloride, phosphorus, non-protein nitrogen, total protein, creatinine, uric acid, and freezing point depression. The urine samples were tested for sodium, potassium, chloride, calcium, phosphorus, ammonia, total nitrogen, creatinine, uric acid, pH titratable acidity, freezing point depression, and, if glycosuria was present, for glucose.

For bicarbonate determination the blood samples were prepared according to Astrup [1], and examined by the method of van Slyke [36]. Sodium and potassium were determined by flame photometry [47], Cl by the method of Volhard [46], P by the method of Fiske and Subbarow [13], ammonia by the method described in [2], creatinine according to Folin and Wu [14], uric acid by Brown's method [2], non-protein nitrogen by the Kjeldahl method, total nitrogen according to Rappaport [40]. The pH was measured by an electric pH meter, the freezing point by means of a micro-Beckmann thermometer. Sugar in the urine was tested according to Hagedorn and Jensen [21]. Acidity was estimated by electrometric titration, titrating with N/10 sodium hydroxide to pH 7.35, under continuous mixing.

In a few cases phenol red excretion was also estimated, using the method described by Stave [44], and modified for infants and small children.

In every case we constructed the blood and urine ionograms and computed all the clearances corrected for 1.73 m^2.* In the urinary ionogram the difference between the found and calculated delta values exceeded 10 per cent in one case only.

In the following we shall discuss the five cases one by one, mentioning briefly the clinical course and laying the emphasis upon the involvement of the kidneys. The practical conclusions will be dealt with separately.

Acute Diffuse Glomerulonephritis

(Sz. M., born, October 19, 1949; admitted, February 19, 1960.)

The acute glomerulonephritis had developed as a complication of scarlet fever. The course had been typical, with oedema, massive haematuria, proteinuria, cylindruria, elevated NPN in blood, reduced urinary delta. The patient after three months of hospital treatment was discharged in a greatly improved condition, but with an essentially chronic residual nephritis.

The results of the serial tests carried out will not be listed here, but be

* Explanation of abbreviations

C_{creat} = creatinine clearance (computed for 1.73 m^2), normal value, 50 to 120 ml.

C_{UA} = uric acid clearance (computed for 1.73 m^2), normal value, 30 to 60 ml.

C_{Na} = sodium clearance (computed for 1.73 m^2), normal value, 0.8 to 3.0 ml.

C_{Cl} = chloride clearance (computed for 1.73 m^2), normal value, 0.8 to 3.0 ml.

C_K = potassium clearance (computed for 1.73 m^2), normal value, 2.0 to 8.0 ml.

C_{OSM} = osmolar clearance (computed for 1.73 m^2) = reduction of freezing point depression of the urine multiplied by minute diuresis and divided by the freezing point depression of serum.

Δ_M = measured depression of freezing point.

$\Delta_{calc.}$ = calculated depression of freezing point.

discussed with the other cases. The data were illustrative of the changes usual in glomerulonephritis. In spite of the marked reduction of glomerular filtration the ability to acidify was retained, the titratable acidity was high, and the urinary ammonia concentration suggestive of satisfactory tubular function. In contrast, the concentrating capacity was insufficient. In spite of the high NPN level, the osmolarity of the urine hardly differed from that of the serum, and the flat curves of phenol excretion were similarly indicative of tubular dysfunction. The data thus revealed a case of retentive kidney, in which the disturbance of glomerular function was the primary and the tubular lesion the secondary change.

Dehydration

(P. A., born October 13, 1959, admitted, February 13, 1960.)

This infant was admitted in a severe state caused by upper respiratory infection associated with moderate dehydration.

After admission, dehydration greatly increased and then the resulting circulatory failure and abdominal distension dominated the picture. In evoking the latter condition, the hypokalaemia must have played an important part. Renal function tests revealed a definite disturbance without organic renal disease. The patient responded to complex treatment (antibiotics, correction of salt and fluid loss) and recovered in three weeks.

The patient was subjected to a detailed examination at the peak of the disease.

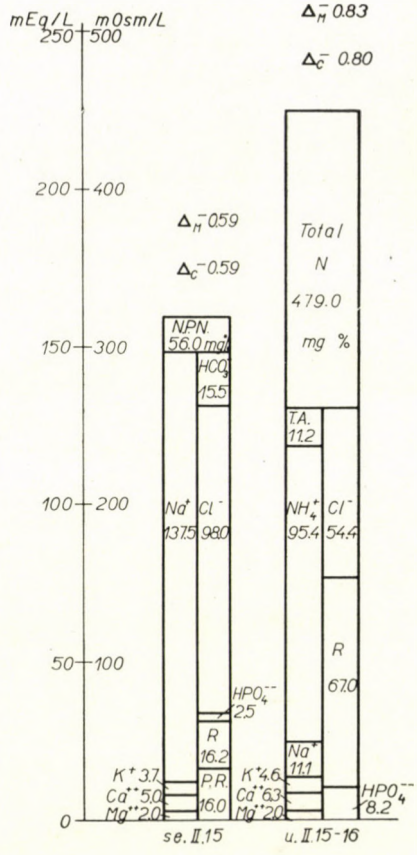

Fig. 1

Clearance tests, urinary pH, glucose excretion

C_{creat}	= 8.45 ml	C_K	= 0.477 ml
C_{UA}	= 2.66 ml	C_{OSM}	= 0.534 ml
C_{Na}	= 0.030 ml	pH	= 6.0
C_{Cl}	= 0.210 ml	sugar	180 mg per 100 ml

In spite of the absence of haematuria, proteinuria, and pathological constituents in the sediment, glomerular filtration was insufficient, as shown by the low creatinine and uric acid clearance.

In spite of the high excretory requirements, the concentrating capacity was weakened and so was the acidifying capacity, as seen from the low titratable acidity value and the pH of the urine.

Ammonia formation seemed intact; acidosis must have been prevented by this function, but its danger is clear from the reduced standard bicarbonate value.

The glycosuria seems to have been due to the tubular lesion rather than to the dextrose contained in the drip infusion.

As a result of the formation of large amounts of ammonia the kidney could retain bases, as indicated by the low base concentration of the urine. It is true, however, that the absolute ammonia output did not much exceed the physiological rate of 1.5 mEq/kg/day [23].

The remarkably high chloride output seems to have served the fight against acidosis.

The results make it clear that in many of its components renal function was impaired, with the lesion mainly in the tubular apparatus.

The detailed analysis of the case suggests that in common dehydration the functional lesion of the kidney and the disturbance in its compensatory activity may aggravate the condition.

Many reports have stressed the importance of studying renal function in cases of acute dehydration. GÖMÖRI, FÖLDI and SZABÓ [19] have shown that in experimental dehydration renal functions are more severely affected than one would expect on the basis of the impairment of circulation.

The azotaemia commonly associated with dehydration has been dealt with in two monographs by KERPEL-FRONIUS [27, 28] whose careful investigations have proved that every type of infantile azotaemia arises from a reduction of renal function, and that in the genesis of extrarenal uraemia not the oliguria, but the diminished renal function resulting from anhydraemia was the decisive factor [29]. This view has been supported by the cases reported by CALCAGNO and RUBIN [7], as well as the detailed data by BLACK [3].

The above case has proved from another angle that in acute dehydration renal failure is not merely a passive result of the haemodynamic disturbance, but the regulatory function of the renal tubules is also impaired.

ACUTE HYPERNATRAEMIC SHOCK

(B. Gy., born July, 1959, admitted January 28, 1960, at 2 p. m.; died January 29, 1960, 7.15 a. m.)

The child had contracted an upper respiratory infection; hyperpyrexia and eclampsia had developed within a few hours. The eclampsia did not respond to the usual methods of treatment and apnoea developed. Tracheotomy was done without delay and under manual artificial breathing the patient was transported to our Department for respirator treatment. The severe eclampsia could be relieved by curare only. The circulatory failure improved for a while, but the patient died in the 21st hour of treatment, after a gradual fall of blood pressure.

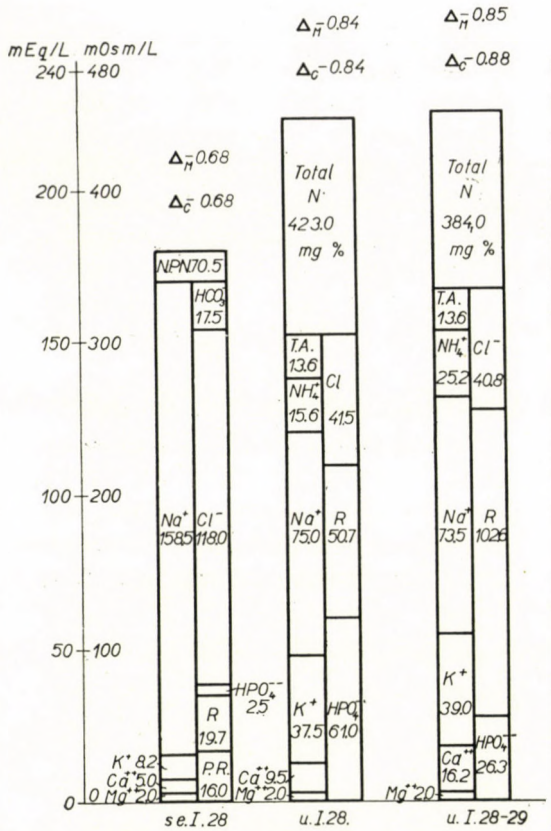

FIG. 2

The tests were made on one occasion, but there were two portions of urine.

Clearance studies, urinary pH values, urinary sugar

I.

C_{creat} ..... = 4.75 ml
C_{UA} ..... = 2.14 ml
C_{Na} ..... = 0.143 ml
C_{Cl} ..... = 0.108 ml
C_{K} ..... = 1.4 ml
C_{OSM} ..... = 0.37 ml
pH (paper) = 6.5
sugar = 320 mg per 100 ml

II.

C_{creat} ..... = 3.65 ml
C_{UA} ..... = 1.43 ml
C_{Na} ..... = 0.10 ml
C_{Cl} ..... = 0.073 ml
C_{K} ..... = 1.02 ml
C_{OSM} ..... = 0.27 ml
pH ..... = 6.07 ml
sugar = 325 mg per 100 ml

This case may be considered one of typical hypernatraemic shock, leading to deatb, probably together with the hyperpotassaemia (serum K, 8.2 mEq/L).

The results of the tests showed a marked decrease of glomerular filtration.

In spite of the high absolute urinary values, the sodium and chloride clearances were low and in spite of the extremely high serum K level the potassium clearance was not excessively low.

The freezing point depression of the serum was remarkable. In spite of the enormous demands, the same cannot be said about the osmolarity of the urine, the $\triangle = -0.84$ value indicating a definitely narrowed concentrating power.

Ammonia formation seems to have been unaffected. Titratable acidity was rather low, the pH just slightly acid, in the urinary ionogram there was a considerable anionic excess.

The lesion to the tubular apparatus followed also from the glycosuria, which could not have been due to the glucose contained in the drip infusion.

Except for the calcium output, the excretion of electrolytes was high,

but still far from the values that would have been required for the correction of the pathological electrolyte balance.

Hypernatraemia is known to occur in the widest variety of conditions (water deficiency, overdosage of electrolytes, renal and endocrine disorders, nervous diseases, etc.). However, even in detailed reviews of the subject, such as that of PRADER and ROSSI [37], no mention is made of the cases in which, like in the one under discussion, the development of hypernatraemia could not be explained by extrinsic disturbances in the electrolyte and fluid supply.

The hypernatraemic forms of infantile dehydration were described by KERPEL–FRONIUS [26] more than two decades ago, and sharply distinguished from the other forms of dehydration. Later RAPPAPORT [39] reported on such cases. The clinical characterisation of the condition as the "hypermotile form" of dehydration has been given by KISS [31] and as "syndrome neurotoxique" by LEVESQUE [34].

Genesis and therapy of hypernatraemic shock have been studied by numerous authors [10, 30, 6, 4, 12, 43] but they have dealt mainly with the electrolyte and fluid balance and the metabolic aspects of the condition

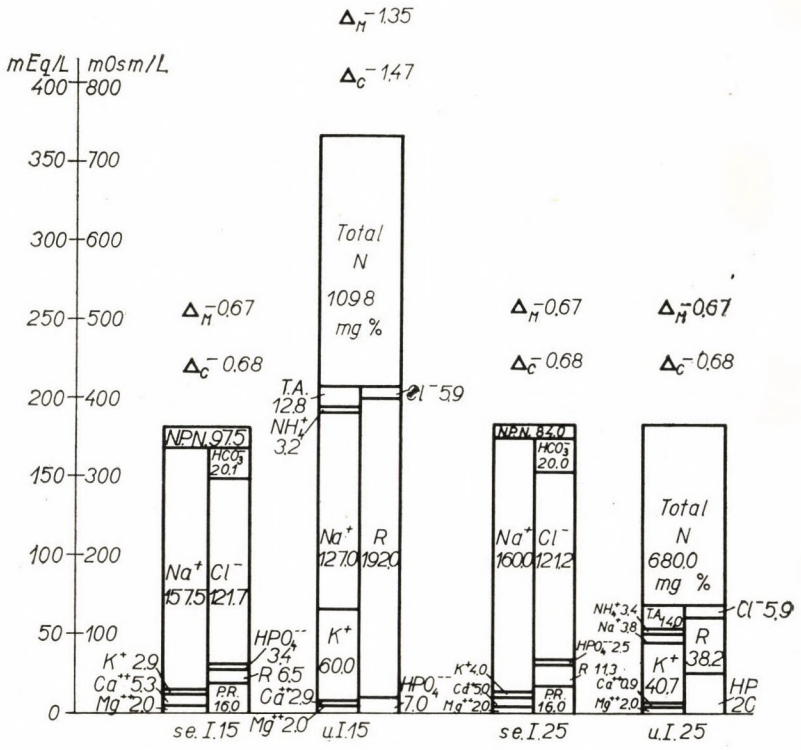

FIG. 3

and, to our best knowledge, did not study renal function.

The above results leave no doubt that renal function was severely impaired in our case. The grave metabolic disturbance, which has been termed by us [5] metabolic cell swelling, and the marked disturbance of renal function might perhaps be traced back to a common factor, a general disturbance of cell metabolism.

Hypernatraemic Encephalitis

(S. M., born February 27, 1954; admitted, January 7, 1960; died, February 21, 1960.)

This patient was admitted in an unconscious state due to measles encephalitis. The course of the disease confirmed the diagnosis made on admission. During the 6 weeks of intermittent positive pressure breathing the vital functions were gradually depressed. Electrolyte metabolism was characterized throughout by extreme hypernatraemia, that could not be relieved by serial salt-free glucose infusions. Renal function deteriorated parallel with the decrease of the other functions. As a result of the gradual impairment of circulation, gangrene developed in one leg and thrombophlebitis in the other, and, in addition, extensive bed sores and corneal destruction.

Clearance, urinary pH values and sugar excretion

I.

C_{creat}	=	7.77	ml
C_{UA}	=	2.88	ml
C_{Na}	=	0.41	ml
C_{Cl}	=	0.025	ml
C_{K}	=	10.9	ml
C_{OSM}	=	1.06	ml
pH	=	5.9	ml

II.

C_{creat}	=	7.2	ml
C_{UA}	=	1.73	ml
C_{Na}	=	0.006	ml
C_{Cl}	=	0.013	ml
C_{K}	=	2.86	ml
C_{OSM}	=	0.28	ml
pH	=	5.0	ml

sugar.....117 mg per 100 ml

Excessive hypernatraemia and hyperchloraemia were associated with hypopotassaemia. The bicarbonate value was normal. Hypernatraemia and hyperchloraemia did not respond to treatment, only the K value became normalized in response to the administration of Darrow's solution.

As indicated by the values for creatinine and uric acid clearance, glomerular function was impaired. But while at the first examination the increase in the serum creatinine and uric acid level was marked, at the second examination the practically unaltered clearance value was the result of the diminution of minute diuresis.

The elevated delta value of the serum was caused not only by the excessive hypernatraemia, but also by the increase of NPN. The concentrating capacity was moderately reduced in the first test and definitely reduced in the second, which is the more remarkable if we realize that the hypernatraemia remained unchanged, in spite of the dextrose infusion.

Although according to the bicarbonate value acidosis was not imminent, ammonia excretion and titrat-

able acidity were still low. The pH of the urine was mildly acid at the first test and definitely acid at the second.

The glycosuria observed in the second period may have been correlated with treatment, although in our experience the usual infusion produces no glycosuria when renal function is intact.

The insufficiency of the tubular apparatus was indicated by the glycosuria, insufficient salt output and by the low Na, Cl and K clearances. The same was revealed by the phenol red excretion curve (made on January 15), which ran a greatly protracted course; after 15 minutes only 0.033 per cent, after 30 minutes 8 per cent, after 60 minutes 23.8 per cent, and at 120 minutes 43 per cent, of the amount administered was excreted.

The laboratory results and their interpretation make it clear that the kidney could not meet the requirements. At autopsy some pus was found in the kidneys, especially the right one. The interval between tests and autopsy was long and as the pyelonephritis developed after the tests had been performed there is little reason to doubt that the pathological functions were correlated with the basic disease (encephalitis).

Hypernatraemia has often been reported to occur in association with lesions to the nervous system, such as injury, encephalitis, apoplexy, cerebral arteriosclerosis, developmental anomalies, etc. In such cases the hypernatraemia is usually induced by dehydration due to water deprivation, or by a failure of covering the fluid requirement. There are, however, cases, e.g. 11 and 45, the former one of cerebral tumour, the latter a case of encephalitis, in which hypersalaemia persisted for a long period in spite of a large fluid intake and sufficient diuresis. The problem, as it occurs in infancy and childhood, has been surveyed by PRADER and ROSSI [37], as well as by PRADER and ISLER [38].

In our case the severe and constant hypersalaemia may have been maintained apart from hormonal factors by a disturbance of the higher nervous centres directly controlling salt and water metabolism, the role of which has been elucidated by Hungarian authors [20, 15, 32, 33]. According to their results, renal sodium output characteristically decreases and sodium reabsorption increases in response to cerebral hypoxia. The role of this mechanism in congestive heart failure may be considered as proved.

ACUTE TUBULAR NECROSIS

(M. M., born, December 27, 1955; admitted, January 21, 1960.)

The patient was transferred to us from the Institute of Postgraduate Medicine in a grave state of septicaemia and toxaemia due to scarlet fever and varicella. (The subsequent course of the disease was followed in cooperation with Dr. B. Steiner.) Both upper and lower eyelids were inflamed and swollen. The flush and swelling extended later to the face and forehead. The ocular process was considered to be due to erysipelas. During the first 10 days the picture was dominated by acute renal failure and its sequelae. Diuresis was re-started by perirenal procaine infiltration, after five days of anuria and oliguria. The initial

anuria lasted five days; it was followed by a period of copious diuresis. During the first half of that period the NPN was still high (early diuretic period), then it became normalized in a few days, with the diuresis still copious (late diuretic period).

In spite of the severe shock the process proved to be reversible and the patient was discharged, after more than five weeks of treatment, in a good condition. There were merely some residual ocular changes. She had gained 2.3 kg.

We made the tests repeatedly, but here we present only the first serum ionogram from the oliguric phase, the third from the early polyuric phase and the fifth from the late polyuric phase

Clearance, urinary pH values, glycosuria

III.

C_{creat}	=	1.96	ml
C_{UA}	=	1.65	ml
C_{Na}	=	0.305	ml
C_{Cl}	=	0.384	ml
C_{K}	=	2.37	ml
C_{OSM}	=	0.53	ml
pH	=	7.1	ml

V.

C_{creat}	=	36.2	ml
C_{UA}	=	22.1	ml
C_{Na}	=	1.03	ml
C_{Cl}	=	1.2	ml
C_{K}	=	11.7	ml
C_{OSM}	=	1.96	ml
pH	=	6.52	
sugar	.....780 mg per 100 ml		

In the oliguric and anuric phases there were marked hyponatraemia and an even more marked hypochloraemia, which persisted throughout the early diuretic phase, in spite of our efforts to increase the salt intake. In the early phase of oliguria, glomerular filtration was greatly diminished. In the early diuretic phase the clearance values increased slowly, but the absolute serum level of creatinine was high. The same was the case with NPN, which reached the highest level by the end of the early diuretic phase. It was remarkable that glomerular filtration was practically normal by the end of the early diuretic phase, which was not the case with tubular function.

The freezing point depression of the serum was normal in the anuric and early diuretic phases, because of the increased NPN and excessive hyposalaemia. The real situation was reflected only after the early diuretic phase, when urinary osmolarity had definitely increased.

Although the value for serum bicarbonate was normal throughout, there was no acidosis (on the contrary, later there was some tendency to alkalosis) and it might have been correlated with this that the urinary pH was alkaline or at least near-neutral in every phase with 5.88 as the lowest pH in test period VII. For this reason the ability to acidify could not be tested; this could have been approached by NH_4Cl loading only, which could not be done considering the grave state of the patient.

Ammonia formation was low until the end of the early diuretic phase and rose slightly at the time of the concentration test.

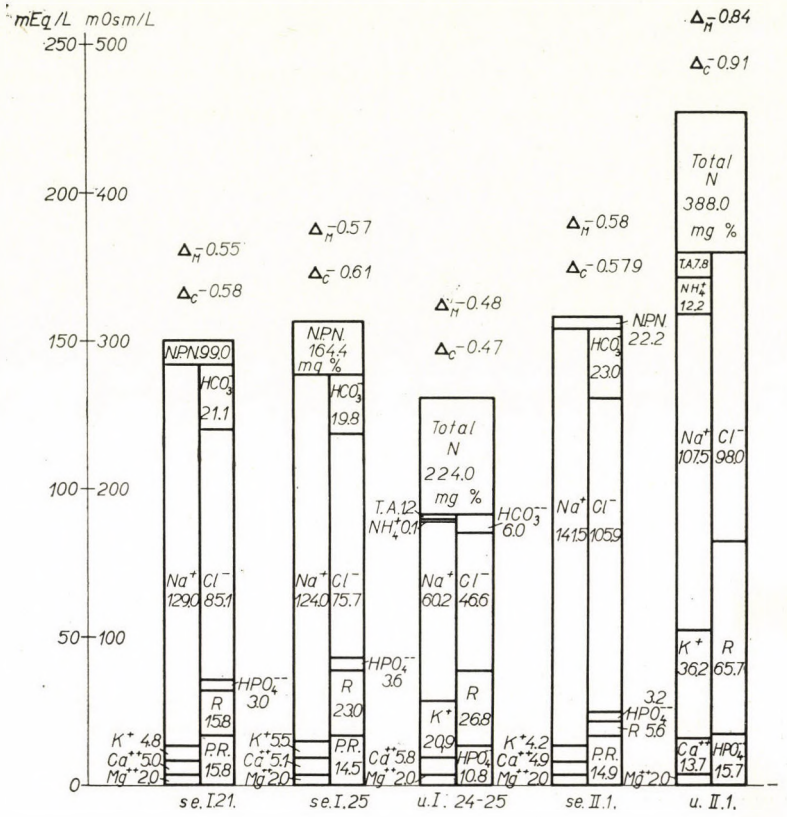

FIG. 4

We are unable to explain satisfactorily the glycosuria found in test period V, since at that time the tubular lesion improved markedly and the infusions had been discontinued.

As already mentioned, there was a considerable hyponatraemia in the serum until the end of the early diuretic phase. In spite of this — obviously due to tubular insufficiency — the kidney was unable to retain bases. The same process was even more obvious in the case of Cl metabolism and the same process may explain the disturbance of potassium excretion, which was especially important as the initially elevated serum K level dropped to hypokalaemia at the time of severe azotaemia. The serum and urinary Ca and P values were nearly normal. The concentration test, except for the bicarbonate value, reflected normal relations.

The phenol red excretion test made on February 10 was also normal (15 minutes, 14 per cent; 30 minutes, 45.2 per cent; 60 minutes, 55.2 per cent; and 120 minutes, 62.7 per cent).

Our case may be considered to be one of typical tubular necrosis, or acute renal failure. Such cases have been denoted by different names in the literature, such as lower nephron nephrosis [35], transfusion kidney, shock kidney, crush syndrome, sublimate nephrosis, tubular nephritis, acute ischaemia, ischaemic nephropathy. In general these terms allude not only to the essence and localization of the process, but to the aetiologic factor as well.

Our case illustrates that the leading features in the process is the hyperacute tubular lesion. The glomerular damage is of minor importance and becomes normal considerably sooner than the tubular lesion.

The commonest eliciting factors are injury, shock due to transfusion or burns, poisonings; acute infection is an uncommon cause [8]. In our case the toxic scarlet fever seems to have been the only factor that might be held responsible for the condition.

Comparing the last case with the first of the series under discussion, the one of typical scarlet fever glomerulonephritis, it is clear that the same factor in the same organ may produce changes widely differing both in course, and as regards prognosis. It is vital for the patient that the two pathological processes should sharply be distinguished.

Acute tubular necrosis has been discussed in many reports and monographs (see for instance 9, 42, 48; and for clinical observations in children 16 and 17).

Practical Conclusions

Our studies may have contributed to the understanding of the pathological processes involved. The tests concerning the most fundamental renal functions such as the concentrating, acidifying base-retaining capacities of the kidney and its other similar functions are usually neglected in practical medicine, even in typical renal disease. An assessment of such renal functional disturbances, however, is undoubtedly of a decisive significance in every condition inducing tubular damage. In such cases retention ceases soon after the oliguric phase, urinary N output increases, but at the same time the kidney is excreting without any control the valuable electrolytes, mainly sodium and potassium. The fate of the patient depends on whether the losses are recognized and suitably replaced in time. Once we look for them, we find these cases to be far from rare; it is especially those with oliguria of a few hours' duration which often escape detection.

The fact seems to be remarkable that essentially the same changes can be demonstrated in acute metabolic disturbances, in the functional insufficiencies believed earlier to be distinct from renal disease, and in extrarenal azotaemia. This statement is based not solely upon the examinations reported in the present paper; apart from their agreeing with some other investigation [22, 24, 25, 40], we have obtained identical results in a number of similar cases.

The functional nature of the disturbances revealed by us is supported by the fact that renal function becomes normal in most cases after the normalization of the systemic metabolic disorder. This recognition places in a different light the observations that sometimes the electrolyte imbalance cannot be explained by a loss of electrolytes and fluids through vomiting or diarrhoea, etc.; in the background of such cases one should always suspect some disturbance of renal function.

The elucidation of the underlying factors may be of some importance even in the so-called irreversible cases. For example, in our case of encephalitis with hypernatraemia the tests greatly contributed to the recognition of the central origin of the metabolic changes. The ineffectiveness of the treatment aimed at relieving these alterations proved only that the primary lesion was not in the peripheral regulatory mechanism, in other words in the kidney, but in the central nervous system. Adequate restoration of the balance may prolong survival even in such cases.

Summary

The disturbances of renal function associated with acute infectious diseases have been studied on the basis of ionograms and electrolyte excretion. Five cases have been discussed, one each of acute dehydration, hypernatraemic shock, encephalitis with hypernatraemia, acute tubular necrosis, and, to facilitate comparison, of acute diffuse glomerulonephritis.

From the analysis of these cases it has been concluded that the different pathological conditions examined may be accompanied by an absence or insufficiency of one or several of those compensatory mechanisms (concentrating, water excreting, acidifying capacity, ammonia formation, base retention, excretion of electrolytes and metabolites), which are characteristic of renal function under normal circumstances. A disturbance of renal function, and within it a disorder of the fine, multidirectional tubular regulation, may be involved in a highly variable manner in the development of the metabolic disturbance accompanying acute conditions.

References

1. Astrup, P.: A Simple Electrometric Technique for the Determination of Carbon Dioxide Tension in Blood and Plasma, Total Content of Carbon Dioxide in Plasma, and Bicarbonate Content in "Separated" Plasma at a Fixed Carbon Dioxide Tension (40 mm Hg). Scand. J. clin. lab. Invest. **8,** 33 (1956).
2. Bálint, P., Hegedűs, A.: Klinikai laboratóriumi diagnosztika. Művelt Nép Kiadó, Budapest 1955.
3. Black, J. A.: Renal Tubular Damage in Infantile Gastroenteritis. Arch. Dis. Childh. **34,** 158 (1959).
4. Boda, D., Galambos, M.: Szervelektrolit vizsgálatok heveny kísérletes széntetrachlorid mérgezésben. MTA. Biol. Orvostud. Oszt. Közl. (Budapest) **8,** 172 (1957).
5. Boda, D., Galambos, M.: Balance Experiments in Cases of Infantile Acute Hypernatraemia. Acta med. hung. **14,** 163 (1959).

6. Boda, D., Kiss, S.: Der Zellstoffwechsel bei Säuglingstoxikose und Atrophie auf Grund der Untersuchung der roten Blutkörperchen. Acta med. hung. **9,** 97 (1956).
7. Calcagno, P. L., Rubin, M. J.: Effect of Dehydration Produced by Water Deprivation, Diarrhea and Vomiting on Renal Function in Infants. Pediatrics **7,** 328 (1951).
8. Carré, I. J., Squire, J. R.: Anuria Ascribed to Acute Tubular Necrosis in Infancy and Early Childhood. Arch. Dis. Childh. **31,** 512 (1956).
9. Cort, J. H., Fencl, V.: Physiologie der Körperflüssigkeiten. Fischer, Jena 1958.
10. Csapó, J., Kerpel-Fronius, E.: Über die Urämiefrage. Z. ges. exp. Med. **92,** 603 (1934).
11. Engel, F. G., Jaeger, C.: Dehydration with Hypernatremia, Hyperchloremia and Azotemia Complicating Nasogastric Tube Feeding. Amer. J. Med. **17,** 196 (1954).
12. Finberg, L., Harrison, H. E.: Hypernatremia in Infants. Pediatrics **16,** 1 (1955).
13. Fiske, C. H., Subbarow, I.: The Colorimetric Determination of Phosphorus. J. biol. Chem. **66,** 375 (1925).
14. Folin, O., Wu, H.: A System of Blood Analysis. J. biol. Chem. **38,** 81 (1919).
15. Földi, M., Solti, F., Rév, J., Szám, J., Koltay, E.: Wirkung der Hypoxie auf die Nierenfunktionen beim Menschen. Acta med. hung. **10,** 43 (1957).
16. Gautier, E.: Behandlung der anurischen Nephropathien. Mschr. Kinderheilk. **106,** 176 (1958).
17. Gautier, E.: Klinik und Therapie der Anurie im Kindesalter. Schweiz. med. Wschr. **17,** 464 (1959).
18. Gláz, E.: Gyors, egyszerű serum Ca meghatározás. Orv. Hetil. (Budapest) **99,** 968 (1958).
19. Gömöri, P., Földi, M., Szabó, Gy.: Vérkeringés és veseműködés. Magy. Belorv. Arch. **5,** 105 (1952).
20. Gömöri, P., Kovách, A., Takács, L., Földi, M., Szabó, Gy., Nagy, Z., Wiltner, W.: A hypoxia és a hypercapnia szerepe a vesevérkeringés idegrendszeri szabályozásában. Magy. belorv. Arch. **7,** 129 (1954).
21. Hagedorn, H. C., Jensen, B. N.: Zur Mikrobestimmung des Blutzuckers mittels Ferricyanid. Biochem. Z. **135,** 46 (1923).
22. Hungerland, H.: Nierenfunktion und Harnionogramm. Mschr. Kinderheilk. **106,** 171 (1958).
23. Hungerland, H., Schulz, R.: Über die Ammoniakausscheidung des Säuglings. Arch. Kinderheilk. **153,** 91 (1956).
24. Hungerland, H., Vogtherr, H., Weber, H.: Zentrale Störungen des Mineralstoffwechsels. Mschr. Kinderheilk. **104,** 147 (1956).
25. Hungerland, H., Weber, H.: Die Bedeutung des Ionogramms des Harns für die Klinik. Dtsch. med. Wschr. **80,** 1341 (1955).
26. Kerpel-Fronius, E.: Über die Wechselbeziehungen zwischen Kochsalz und Reststickstoff. Z. ges. exp. Med. **85,** 235 (1932).
27. Kerpel-Fronius, E.: Salzmangelzustände und Chloroprive Azotaemie. Ergebn. inn. Med. Kinderheilk. **51,** 623 (1936).
28. Kerpel-Fronius, E.: Die pathologische Physiologie toxischer Zustände im Säuglingsalter. Ergebn. inn. Med. Kinderheilk. **61,** 919 (1942).
29. Kerpel-Fronius, E., Varga, F., Vönöczky, J.: The Relationship between Circulation and Kidney Function in Infantile Dehydration and Malnutrition. Acta med. hung. **5,** 27 (1954).
30. Kerpel-Fronius, E.: Pathologie und Klinik des Salz- und Wasserhaushaltes. Akadémiai Kiadó, Budapest 1959.
31. Kiss, P.: Weitere Beiträge zur Frage der akuten Coronarkreislaufstörung im Säuglingsalter. Arch. Kinderheilk. **125,** 124 (1942).
32. Kovách, A. G. B., Földi, M., Papp, M., Koltay, E.: Wirkung von Dibenamin und Adrenektomie auf die hypoxische Hyponatriurie. Acta med. hung. **10,** 25 (1957).
33. Kovách, A. G. B., Földi, M., Papp, N., Roheim, P. S., Koltay, E.: Cerebral Regulation of Sodium Excretion. Lancet **1,** 338 (1959).
34. Levesque, J., Bastin, R., Lefourcade, J.: Les toxicoses du nourrisson I. — Pathogénie et étiologie des toxicoses du nourrisson. Sem. Hôp. Paris **25,** 3716 (1949).
35. Lucké, B.: Lower Nephron Nephrosis (Renal Lesions of the Crush Syndrome, of Burns, Transfusions, and other Conditions Affecting Lower Segments of Nephrons). Milit. Surg. **99,** 371 (1946).
36. Peters, J. P., van Slyke, D. D.: Quantitative Clinical Chemistry. Williams and Wilkins, Baltimore 1946.
37. Prader, A., Rossi, E.: Hyperelektrolytaemie (Hypertonie und Hyperosmie der Körpersäfte) bei Wassermangel, Elektrolytüberdosierung, renalen und endokrinen Störungen. Helv. paediat. Acta. **4,** 482 (1946).

38. Prader, A., Isler, W.: Chronische neurogene Hyperelektrolytaemie infolge praenataler Hirnschädigung. Helv. paediat. Acta. **9,** 264 (1954).
39. Rapoport, S.: Hyperelectrolytemia and Hyperosmolarity in Pathologic Conditions of Childhood. Amer. J. Dis. Child. **74,** 682 (1947).
40. Rappaport, F.: Verfeinerung der maßanalytischen Bestimmung des Rest-N im Blute ohne Destillation. Klin. Wschr. **16,** 1190 (1937).
41. Rosenkranz, A.: Über Untersuchungen der renalen Elektrolytausscheidung zur Beurteilung einiger tubulärer Nierenfunktionen. Mschr. Kinderheilk. **106,** 199 (1958).
42. Schwartz, R., Tomsovic, E. J., Schwartz, J. L.: Hyperpotassemia and Body Water Distribution in an Anuric Child. Pediatrics **7,** 516 (1951).
43. Skinner, A. L., Moll, F. C.: Hypernatremia Accompanying Infant Diarrhea. Amer. J. Dis. Child. **92,** 562 (1956).
44. Stave, U.: Beitrag zur funktionellen Reifung der Nierentubuli: die Phenolrot-Ausscheidung in Säuglingsalter. Z. Kinderheilk. **77,** 554 (1956).
45. Ullmann, T. O.: Hyperosmolarity of the e. c. Fluid in Encephalitis with Report of a Case. Amer. J. Med. **15,** 885 (1953).
46. Volhard, J.: Z. anal. Chem. **17,** 482 (1878) cit.
Volhard, F., und Becher, E.: Die klinischen Methoden der Nierenfunktionsprüfung. Springer, Berlin 1929.
47. Zak, B., Robert, E., Mosher, D., Albert, J., Boyle, M. D.: A Review on Flame Analysis in the Clinical Laboratory. Amer. J. clin. Path. **23,** 60 (1953).
48. Zuelzer, W. W., Charles, S., Kurnetz, R., Newton, W. A., Fallon, R.: Circulatory Diseases of the Kidneys in Infancy and Childhood. Amer. J. Dis. Child. **81,** 1 (1951).

Dr. M. Galambos
Gyáli út 5.
Budapest, IX., Hungary